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**FDA Public Meeting  
“Direct to Consumer Genetic Testing”  
March 8-9, 2011**

Comments submitted by  
Robert C. Green, MD, MPH

**INTRODUCTION AND QUALIFICATIONS**

I appreciate the opportunity to comment on direct-to-consumer genetic testing. To briefly summarize my background, I am a physician-scientist who is board certified in neurology and board-eligible in medical genetics, and whose research focus has moved from clinical trials and genetic epidemiology of Alzheimer's disease (AD) to more general topics of clinical genomics and health outcomes across a wide spectrum of disorders. I have been continuously funded by NIH for 21 years and have published over 300 articles. My specific contributions to genetics and genomics have included the development of risk estimates based on family history and genetic markers in AD,<sup>1,2</sup> analysis of large multi-center treatment and prevention trials, including trials enriched through family history,<sup>3-5</sup> and design, leadership and future planning of some of the early randomized clinical trials in translational genetics.<sup>6-8</sup> I serve on a number of advisory, editorial and grant review boards and am a regular member of the NIH study section previously called Ethical, Legal and Social Implications of Human Genetics (now Clinical, Genetic and Research Studies). I have been invited

to participate in NIH planning workshops on the future of genomic medicine,<sup>9</sup> and have been a featured or plenary speaker at the World Science Festival, the National Coalition of Health Care Professionals for Education in Genetics, the American Academy of Neurology, the Consumer Genomics Conference, the World Congress on Psychiatric Genetics, the American Society for Human Genetics, the National Press Club and the BioIT World Conference. I am a Board Member of the Council for Responsible Genetics and will be a plenary speaker on the topic of “Translational Genomics” at this year’s Presidential Symposium of the 2011 American College of Medical Genetics.

My work is thus directly relevant to the issues under consideration at this meeting of the FDA. I am the director of the REVEAL Study (R01-HG02213 funded 1999-2013), having built a team of clinicians, geneticists, genetic counselors, health psychologists, ethicists and policy scholars to conduct 4 separate multi-center randomized clinical trials that have collectively enrolled over 1100 individuals to explore issues that arise for patients and health professionals in the disclosure of genetic results. Reports from the REVEAL Study have used APOE genotype and risk of AD to explore how individuals understand genetic risk, what they do with the information, and how it makes them feel. This includes studies in different ethnic groups,<sup>2, 10-12</sup> with particular attention to African Americans, and explicit assessment of the emotional impact that can accompany disclosure of risk information,<sup>6, 13-17</sup> the reasons people seek genetic risk information,<sup>18, 19</sup> issues in self-perception of risk and how these change with genetic testing,<sup>20-23</sup> the degree to which participants recall their test results or discuss them with others,<sup>24-26</sup> the degree to which genetic testing affects insurance purchasing,<sup>27, 28</sup> and the degree to which genetic testing alters health behaviors.<sup>17, 29-31</sup> I have also written about the scientific and social aspects of direct-to-consumer genetic testing,<sup>32-35</sup> and I direct (with joint-PI Dr. Scott Roberts at University of Michigan) the first NIH study (R01-HG005092) to prospectively examine the impact of consumer-based personal genomics services. I am a frequent collaborator with both early and established investigators in genetics and genomics from around the country, including ongoing studies disclosing genes for obesity (C. Wang, PI, HG00603) and diabetes (R. Grant, PI, DK084527), the Gene Partnership Program (I. Holms, PI, HG005491), the Coriell Personalized Medicine Collaborative (M. Christman, PI), the Working Group on Incidental Findings in Genomic Biobanks (S. Wolf, PI, HG003178) and on Harvard’s Center for Excellence in Genome Sciences (G. Church, PI, HG003170).

## **POTENTIAL CONFLICTS OF INTEREST**

Over the course of my career, my research funding has been almost entirely from National Institutes of Health with occasional paid consultation to, or speaking for, pharmaceutical companies unrelated to this topic. I have no financial conflicts of any kind on this topic. My recently funded NIH grant (R01-HG005092) on the impact of DTC testing involved initial negotiations with Navigenics,

23andMe, DeCodeMe and Pathway, and two of those companies (23andMe and Pathway) have elected to participate in the study at this time. I have not accepted any grant funding or personal compensation or equity from these or from any DTC company or genetics-related company or advocacy group, nor have I been promised any position, compensation or equity from any such concern in the future.

## **COMMENT**

As a scientist who has studied the impact of disclosing genetic susceptibility tests for over 10 years and as a medical geneticist, I write to ask you to consider the following points:

- Most of the information provided by DTC companies is derived from genetic risk markers based on GWAS studies (susceptibility markers based on statistical analysis of variations common among human populations). These sample only common variants and offer modest predictive information that is based mainly upon known genetic markers. In the absence of family and personal history, and in the absence of other, as yet unknown genetic variations, this risk information may be inaccurate in determining the overall risk of a particular disease. Thus two individuals with the same genetic markers might receive the same risk assessment for diabetes, even if one is morbidly obese with a family history of diabetes and the other is thin without any such family history. If customers misunderstand what DTC services are offering, or DTC companies are not clear in communicating limitations in what they are providing, customers may be falsely encouraged or falsely reassured and act in ways that may be detrimental to their health. However, there is little direct evidence of benefits or harms.
- Our research (cited above) suggests that there are few psychological risks to allowing individuals to get genetic susceptibility testing on their own. While these initial studies have not definitively established the safety of disclosing genetic risk information, they do suggest that people who are motivated to seek out genetic testing for themselves are generally well-prepared psychologically to receive the information and do not have negative reactions to it, regardless of what they learn. Some studies do show a transient elevation of indicators of psychological distress, but these are generally mild and they return to baseline. Several studies show a benefit to those who learn their risk is lower than average, and that benefit persists in comparison to either those who don't get tested at all or those who get "bad news" that they are at elevated risk. Therefore, the risks of allowing individuals to obtain this information without physician intervention appear small and there do appear to be benefits for those who get "good news."

- Beyond this, the benefits of providing risk information via DTC genetic testing have yet to be established. However, our research suggests that learning about increased risk can modify behavior, for example by motivating individuals to more closely monitor their health status or to get more exercise.
- Currently most DTC companies focus upon genetic markers derived from GWAS studies that provide modest risk estimates for common complex disorders such as heart disease or diabetes. The evidence suggests that these modest risk differences are not particularly meaningful in terms of moving individuals from one risk category to another, such that recommended medical interventions would be changed. Therefore, any medical benefit or “clinical utility” to be gained through DTC services is modest at best. Our work has emphasized, however, that people get significant personal satisfaction and personal benefit or “personal utility” from exploring their own genetic information and better understanding their own risk information. That is, the benefits of much of this information may be about paying more attention, learning more, and satisfying curiosity – ie, awareness as much or more than “medical” benefit.
- Some DTC companies are already moving to provide variants for Mendelian disorders such as common pathogenic variants of BRCA1/2. This has the potential for misunderstanding if customers feel that screening for the most common variants exempts them from the possibility of carrying less common variants. While this has the potential for harm through misunderstanding, it may have public health benefit as well. Many disease-causing variants will not be suspected through family history, so that voluntary population screening through medical professionals or through DTC vendors may be the only way in which some at-risk individuals could be discovered and seek appropriate consultation. Some of those at risk will only be detected because they got their genome scanned. Potential harms should be weighed against the potential for benefit with empirical research. The key clinical issue here is making sure that customers know to confirm the results and get attention from a health professional before seeking surgery or other high-risk interventions.

My opinions on some of the issues surrounding DTC companies are as follows:

- I have published, with Dr. Jim Evans, an editorial calling for collaborative engagement between medical establishment and DTC companies.<sup>34</sup> I believe that this is in the best interests of both entities and of society. I have attached this editorial with this statement and

ask that it be included in my statement.

- Some DTC companies operate at a high standard of scientific rigor in approaching health issues and ancestry, aligning themselves with advisors who are respected professionals in genetics and genomics, and bringing a high degree of research and reflection to the information they provide. Others, such as those promising genomic approaches to romance, beauty products or nutrition, are patently fraudulent. In my own area, for example, Navigenics assesses AD risk and has counseling services available, but another company, Graceful Earth, purports to offer similar testing, along with testing dog hairs and nutritional status, and has no association with health professionals. While there should be mechanisms to investigate and regulate fraudulent companies, those that are maintaining high standards of scientific quality are providing information that consumers are willing to pay for and that medical science is unable or unwilling to provide. Therefore, I favor regulation that could distinguish fraudulent from responsible practices, but suggest caution before overly regulating services that have high standards and strong affiliations with medical professionals.
- As with any business, DTC companies should be held accountable for untrue statements used in promoting their services, particularly health claims. This becomes even more important when reporting highly potent medical information such as inherited risk of cancer.
- There are not enough trained geneticists or genetic counselors to meet the needs of a populace that is increasingly interested in genetics. Responsible DTC companies, working with respected clinicians in most cases, have been among the first in our society to attempt to interpret and empower ordinary people to understand genetics and take responsibility for health maintenance and disease prevention. It seems clear, at the dawn of low-cost ways to sequence entire genomes, that more and more genomic information will be available all around us. We surely need new services, well beyond the current capacity of my field of medical genetics, to address the interpretation and communication of such information. The pioneering firms in personal genomics have been innovative in their approach to informatics and health communication, providing avenues for customers to inform themselves on topics and issues that traditional medical care system has not provided. They bring a “web” mentality that resonates in the Internet Age, in contrast to our sometimes stodgy and consistently expensive health care system that is struggling even to adopt a digital medical record.
- Some DTC companies have signaled their intention to move toward whole-exome or whole

genome sequencing and interpretation, that is, to sequence all of a person's genome, or at least the parts that encode proteins and are therefore likely to affect biological function. There is considerable potential for confusion about finding genetic changes that can cause disease, especially if they are "private" mutations or are identified without the context of family history. While current practices in DTC genomics, which report mostly common variants and fairly weak clinical impact are fairly innocuous, the potential for confusion, misunderstanding and harm will increase as DTC companies move into sequencing. Some genetic changes are likely to be both high impact and rare, which means they may be clinically important, but will be a challenge to identify and corroborate scientifically. Such information is highly potent, just like a drug, and raises concerns about safety and downstream costs.

- We do not have accurate measures of the actual health and psychological benefits and harms of disclosing genetic information through DTC companies. The National Human Genome Research Institute and other funders have supported studies to examine this, and several of the DTC companies have participated in them. I am involved with one such study, and in that case, 23andMe and Pathway have relinquished any control over data analysis or reporting. The results of these studies should be carefully evaluated so that empirical findings can inform any debate about the appropriateness of DTC testing. I think it is better to know than not to know, and independent studies by those who are not direct stakeholders are perhaps the best way to learn what works and does not, how people react to information, and whether those getting tested think the process is worthwhile and safe.

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